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DIEHL SERVILLA LLC 33 WOOD AVE SOUTH SECOND FLOOR, SUITE 210 ISELIN, NJ 08830			EXAMINER MUMMERT, STEPHANIE KANE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No. 09/802,162	Applicant(s) GETTS, ROBERT	
	Examiner STEPHANIE K. MUMMERT	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17,27,28,31,32,35,36,39 and 41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17,27,28,31,32,35,36,39 and 41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed on August 13, 2010 is acknowledged and has been entered. Claim 1 has been amended. Claims 18-26, 29-30, 33-34, 37-38, 40 and 42 have been cancelled. Claims 1-17, 27-28, 31-32, 35-36, 39 and 41 are pending.

Claims 1-17, 27-28, 31-32, 35-36, 39 and 41 are discussed in this Office action.

All of the remaining amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL as necessitated by Amendment.

Previous Grounds of Rejection

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/187681, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, for claims 28 and 32, the prior filed provisional application does not disclose the use of at least three different capture sequences as part of multiple channel analysis. Instead, the specification of the prior filed application only makes reference to “3DNA™ expression array reagents are available with either Cy3™ or Cy5™ attached to the 3DNA™ molecule, making possible either single or dual channel detection in array experiments” (p. 1 of prior filed application). Therefore, due to the failure to provide adequate support for these claims, as currently amended, claims 28 and 32 are being afforded the effective filing date of the instant application, filed March 8, 2001.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 27-28, 31-32, 35-36, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 includes step “5) wherein said first component comprising cDNA reagents is hybridized in a single step to both said microarray and to said second component comprising

dendrimer". This step is not supported by the specification or by the claims as originally filed. The specification teaches, at most, pre-hybridization of the first and second components (the cDNA and dendrimer), followed by hybridization to the array (see Figure 2). Regarding the issue of a single step of hybridization, the specification states "The hybridization speed and efficiency is greatly enhanced by **first hybridizing the cDNA to the dendrimer probes before hybridizing the cDNA to the microarray**. This single-step hybridization process also reduces the number of hybridization buffers to one by eliminating the use of a cDNA hybridization buffer" (paragraph 56, emphasis added). The passage cited above does not teach a single step of hybridization, it teaches a first step of pre-hybridization, followed by hybridization to the array. There is no other teaching in the specification which supports the mixing or hybridization of the components on the array.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. Claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN 5, 487,973; January 1996) and Ranki et al. (US Patent 4,563,419; January 1986). Sampson teaches a method for the amplification of the signal of target sequences using a bidirectional primer and cDNA synthesis (Abstract).

With regard to claim 1, Sampson teaches a method for detection and assay on a microarray, comprising:

1) taking a microarray having thereon a plurality of features each comprising a first particular first nucleotide sequence (p. 9, lines 28 to p. 10, line 3, where tagged cDNA is hybridized to the surface of an array; p. 1, lines 10-15, p. 7, lines 19-23 and p. 16, lines 16-18, where the type of array is described as comprising nucleic acid),

2) taking a first component comprising cDNA reagents having a capture sequence comprising a label providing a directly detectable signal (Figure 1, where cDNA is generated that comprises a 3' sequence that provides a 'capture' sequence; p. 9 lines 4-26, specifically steps 1 and 2, where the target mRNA is transcribed into cDNA using a bidirectional primer that generates a repeated signal amplification sequence with fluorescent labels or, see p. 11, lines 21-22, where it is contemplated that second half of the bidirectional primer is an aptamer for the purpose of generating signal amplification of the target w/ the aptamer attached; or see p. 16, lines 7-10, where signal amplification may be achieved by hybridizing a fluorescently tagged probe to the defined sequence added by the bidirectional primer); and

wherein said cDNA reagents comprise a plurality of different nucleotide sequences, and wherein said capture sequence of cDNA reagents is a common sequence among said cDNA reagents, said common sequence being complementary to the nucleotide sequence of said aptamer or signal amplification unit (Figure 1, where the bidirectional primer comprises a sequence that is common to all cDNA targets and which is complementary to the circular probe which generates a repeated signal amplification sequence with fluorescent labels or, see p. 11, lines 21-22, where it is contemplated that second half of the bidirectional primer is an aptamer for the purpose of

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generating signal amplification of the target w/ the aptamer attached; or see p. 16, lines 7-10, where signal amplification may be achieved by hybridizing a fluorescently tagged probe to the defined sequence added by the bidirectional primer);

3) mixing said first and second components at a temperature and for a time sufficient to enable said first component to bind to said second component (Figure 1, step 2, where the cDNA reagent is combined with a second component); and

4) incubating this mixture with said microarray at a temperature and time sufficient to enable the first nucleotide sequences to bind to said first component, wherein said binding results in the generation of a hybridization pattern on the microarray (p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected);

5) wherein said first component comprising cDNA reagent is hybridized to both said microarray and to said second component, while said first component comprising cDNA is on said microarray (Figure 1, step 2, where the cDNA reagent is combined with a second component; p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected; and where the hybridization between the cDNA and the array occurs as a single step).

With regard to claim 2, Sampson teaches the method of claim 1, wherein said cDNA reagents are obtained from mRNA of a target sample and further comprising the step of forming the first component comprising the cDNA reagent by contacting the mRNA with a quantity of a RT primer having the capture sequence, and with a reverse transcriptase, and nucleotide under conditions sufficient for initiating reverse transcription of the mRNA into said cDNA reagents (Figure 1, where cDNA is generated that comprises a 3' sequence that provides a 'capture'

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sequence; p. 9 lines 4-26, specifically steps 1 and 2, where the target mRNA is transcribed into cDNA using a bidirectional primer).

With regard to claim 10, Sampson teaches an embodiment of claim 1, further comprising scanning the microarray for detecting the detectable signal and the hybridization pattern generated (p. 9, lines 28 to p. 10, line 9, where tagged cDNA is hybridized to the surface of an array and the signal generated is detected).

With regard to claim 35, Sampson teaches an embodiment of claim 1, wherein said capture sequence comprises more than one type of base (p. 9, lines 23-26).

With regard to claim 36, Sampson teaches an embodiment of claim 1, wherein said capture sequence comprises adenine, guanine, cytosine and thymine bases (p. 9, lines 23-26).

With regard to claim 39, Sampson teaches an embodiment of claim 1, wherein said method is used for expression analysis (p. 1, lines 12-15, where arrays are useful for expression analysis).

Regarding claim 1-2 and 41, Sampson does not teach use of dendrimer nucleotide sequences comprising at least one first arm comprising a label and at least one second arm having a second nucleotide sequence, or that the second component comprises a dendrimer nucleotide sequence. Furthermore, while Sampson teaches microarray formats for detection, Sampson does not teach detection of dendrimers bound to an array and does not teach that the mixing of each of the components occurs on the array. Nilsen teaches detection of nucleic acids using dendrimeric probes (Abstract).

Regarding claims 1-2 and 41, for detecting a specific nucleic acid in a target sample using a dendrimeric probe wherein Nilsen et al. teach that the method comprises (i) contacting a first

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set of dendrimer sequences shaped into the form of "DNA beads" (col. 13, lines 3-9, see Figure 3 and 5, where the bead is depicted as a sphere with capture probes) to a target nucleic acid (DNA or RNA) having a capture sequence and a second dendrimer component comprising a dendrimer in the form of a DNA bead having at least one arm with a nucleotide sequence complementary to the capture sequence of the first component (see column 14, lines 30-35, column 15, lines 37-63); (ii) mixing the dendrimer components with the target at a temperature to form a bridge between the two components to enable the cross-linking of first component to the second (see step 1, col. 15, lines 38-41; Figure 5, where the dendrimer component "beads" are cross-linked before binding to the microarray); and incubating the bound mixture with the microarray (col. 15-16, step 2, lines 65, where bead A anneals to the solid support) and detecting signal as an indication of the binding of the target sequence to the specific probe sequence on the bead and results in the generation of a directly detectable hybridization pattern on the micro array (see col. 15, column 16, lines 12-67, column 18, lines 27-51), wherein the step of hybridization of the first component DNA and the second component dendrimer are hybridized to the microarray in a single step (col. 15-16, step 2, lines 65, where bead A hybridizes to the solid support in a single hybridization step).

With regard to claim 5 and 9, Nilsen teaches an embodiment of claim 1, wherein the temperature sufficient to enable the second component to bind to the first component is from about 50 to about 55°C (col. 20, lines 24-44, where the components including the dendrimers bind for 37°C, which is about 50°C), and wherein the microarray and the mixture are incubated overnight at the temperature from about 42 to 65°C in a humidified chamber (col. 20, lines 24-44, where the components including the dendrimers bind for 37°C, which is about 42°C).

With regard to claim 7-8, Nilsen teach that the method comprises annealing times ranging from 8 minutes (see column 20, lines 24-44) to overnight (see column 3, lines 49-60).

With regard to claim 10, Nilsen teaches an embodiment of claim 1, further comprising scanning the microarray for detection of hybridization pattern includes detecting the detectable signal (see column 20, lines 38-40).

With regard to claim 11, Nilsen teaches an embodiment of claim 1, further comprising washing the microarray to purge dendrimers unattached to the microarray after the incubation of the microarray and the mixture (see column 20, lines 35-37).

With regard to claim 13, Nilsen teaches an embodiment of claim 1, wherein the method comprises hybridization buffer (see column 19, lines 14-26; col. 20, lines 60-64, where the hybridization buffer comprises the components of NaPO₄, EDTA and SSC).

Furthermore, while Nilsen doesn't teach the same concentrations of components of the wash buffer as claimed, Nilsen states that the conditions can be varied and an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and buffer component elements and concentrations could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific wash buffer was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Regarding claim 1, neither Nilsen nor Sampson teach that the cDNA and dendrimer are simultaneously hybridized to the array in a single step. Ranki teaches a single step of sandwich hybridization (Abstract).

With regard to claim 1, Ranki teaches 3) mixing said first and second components on said microarray at a temperature and a time sufficient to enable said first component to bind to said second component (col. 2, lines 25-49, where a first DNA fragment is captured onto a nitrocellulose membrane, interpreted as equivalent to the microarray, and where a second DNA fragment is labeled for detection, interpreted as equivalent to the dendrimer of Nilsen and where a target strand, interpreted as equivalent to the cDNA of Sampson are mixed together in one step to allow for a duplex to form between the capture probe and the target and the target and the labeled probe; see col. 5-7, where the details of each component are described in greater detail); and

4) incubating this mixture with said microarray at a temperature and time sufficient to enable the first nucleotide sequences to bind to said first component, wherein said binding results in the generation of a hybridization pattern on the microarray (col. 2, lines 25-49, where a first DNA fragment is captured onto a nitrocellulose membrane, interpreted as equivalent to the microarray, and where a second DNA fragment is labeled for detection, interpreted as equivalent to the dendrimer of Nilsen and where a target strand, interpreted as equivalent to the cDNA of Sampson are mixed together in one step to allow for a duplex to form between the capture probe and the target and the target and the labeled probe; see col. 5-7, where the details of each component are described in greater detail; col. 7, lines 20-25, where the hybridization between

the support/array, the target and the label occurs in a single step at 37°C; col. 7, lines 35-46, where the hybridization pattern on the support is detected following a washing step);

5) wherein said first component is hybridized in a single step to both said microarray and to said second component, while said first component is on said microarray (col. 2, lines 25-49, where a first DNA fragment is captured onto a nitrocellulose membrane, interpreted as equivalent to the microarray, and where a second DNA fragment is labeled for detection, interpreted as equivalent to the dendrimer of Nilsen and where a target strand, interpreted as equivalent to the cDNA of Sampson are mixed together in one step to allow for a duplex to form between the capture probe and the target and the target and the labeled probe; see col. 5-7, where the details of each component are described in greater detail; col. 7, lines 20-25, where the hybridization between the support/array, the target and the label occurs in a single step at 37°C).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method of microarray hybridization with signal amplification taught by Sampson to incorporate the method for detecting a nucleic acid sequence using a dendrimer sequence as taught by Nilsen et al. to arrive at the claimed invention with a reasonable expectation for success. Nilsen et al. states that “background noise could be generated in conventional assay not only from binding to a solid support, but also from binding of the probe to nonhomologous DNA sequences. An open branching of a dendrimeric DNA have many degrees of freedom in their movement relative to each other and have a high avidity for DNA that is complementary to the non-annealed single stranded sequences (see column 18, lines 14-26, column 7, lines 14-19). Furthermore, the method taught by Sampson is directed specifically to “a method of amplifying the signal of a target nucleic acid sequence” (p. 4, lines 27-28) and

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Sampson also teaches “the method of the invention may be used to generate a defined repeated DNA sequence containing only the four naturally-occurring bases where signal amplification may be achieved by hybridizing a fluorescently tagged probe to this defined sequence” (p. 16, lines 6-15). Therefore, the two methods are directed to different but related methods of achieving signal amplification of target nucleic acid sequences using fluorescence and an ordinary practitioner would have been motivated to adjust the method of Sampson to include the dendrimeric probe as taught by Nilsen et al. in order to achieve the expected advantage of developing a sensitive method for detecting a target nucleic acid with a reasonable expectation for success.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Nilsen and Sampson to include the single step of sandwich hybridization taught by Ranki to arrive at the claimed invention with a reasonable expectation for success. While Sampson teaches the array and the capture common sequence and Nilsen renders detection using a dendrimer probe, neither specifically teaches a single step of hybridization of each element. Ranki teaches a single step of sandwich hybridization. Specifically, Ranki teaches that a first DNA fragment is captured onto a nitrocellulose membrane, or the microarray of Sampson, and where a second DNA fragment is labeled for detection or the dendrimer of Nilsen and where a target strand, the cDNA of Sampson and provided. Ranki teaches these three components are mixed together in one step to allow for a duplex to form between the capture probe and the target and the target and the labeled probe which results in a hybridization pattern. As taught by Ranki, “The single-stranded nucleic acid hybridizes with a combination of purified nucleic acid reagents, one of which is labelled and one

of which is affixed to a solid carrier. Hybridization occurs in a single step and typically at a temperature of 37° C. over a period of 16-20 hours” (col. 7, lines 20-25). Ranki also teaches that “The present invention is an improvement over the two-step hybridization technique” (col. 1, lines 61-63) and “[b]ecause of this fact the one-step sandwich hybridization technique is more sensitive than the two-step sandwich hybridization technique. Furthermore, it is more rapid to perform and requires less hybridization mixture and washing solution. Consequently the one-step sandwich hybridization technique is more suitable for routine diagnostics” (col. 2, lines 16-22). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Nilsen and Sampson to include a single step of sandwich hybridization taught by Ranki to arrive at the claimed invention with a reasonable expectation for success.

2. Claims 3-4, 16-17, 19 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN. 5, 487,973; January 1996) and Ranki et al. (US Patent 4,563,419; January 1986) as applied to claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 above, and further in view of Combates et al. (US Patent 6,045,998; April 2000).

With regard to claim 16-17 and 25-26, Nilsen teaches an embodiment of claim 3 and 23, wherein the purging step further comprises the use of a hybridization chamber or station (col. 20, lines 20-33).

However, neither Nilsen, Sampson nor Ranki teaches the use of a spin column to remove unhybridized RT primer. Combates teaches the exclusion of excess RT primer prior to the use of cDNA in downstream applications.

With regard to claim 3 and 23, Combates teaches an embodiment of claim 2 and 22 further comprising the step of purging excess unhybridized RT primer from said first component prior to incubation of said mixture (col. 9, lines 33-38, where excess oligo-d(T), which is used as an RT primer at col. 9, lines 1-4, is removed by chromatography on a spin column).

With regard to claim 4, 19 and 24, Combates teaches an embodiment of claim 3 and 23, wherein the purging step further comprises the step of passing the first component through a spin column media to remove excess RT primer (col. 9, lines 33-38, where excess oligo-d(T), which is used as an RT primer at col. 9, lines 1-4, is removed by chromatography on a spin column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Sampson to incorporate the step of removing excess reverse transcriptase primer as taught by Combates to arrive at the claimed invention with a reasonable expectation for success. As taught by Combates, “contaminating oligo(dT) primer was removed by chromatography on a spin column” (col. 9, lines 33-38) prior to further downstream processing including amplification of the cDNA and electrophoresis. Therefore, considering the teachings of Combates where excess RT primer was removed prior to further analysis of the synthesized cDNA and considering the focal role the bifunctional RT primer plays in the method taught by Sampson in view of Nilsen, one of ordinary skill in the art at the time the invention was made would have been motivated to include the step of RT primer

removal taught by Combates into the method of signal amplification taught by Sampson and Nilsen to arrive at the claimed invention with a reasonable expectation for success.

3. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN 5, 487,973; January 1996) and Ranki et al. (US Patent 4,563,419; January 1986) as applied to claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 above, and further in view of Kool et al. (US Patent 5,714,320; February 1998). Sampson teaches a method for the amplification of the signal of target sequences using a bidirectional primer and cDNA synthesis (Abstract).

Sampson in view of Nilsen and Ranki teach all of the limitations of claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 as recited in the rejection stated above. However, while Sampson teaches hybridization of the second end of the bidirectional primer to the circular signal amplifying template (Figure 1, p. 9, lines 15-17), Sampson does not specify the hybridization temperature. Kool teaches hybridization of a nucleic acid probe with a circular nucleic acid (Abstract).

With regard to claim 6, Kool teaches an embodiment of claim 1, wherein the temperature sufficient to enable the first component to bind to the first nucleotide sequence is from 42 to 65°C (col. 13, lines 13-22, where the temperature of the reaction mixture during rolling circle is about 20-90 °C).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the specific hybridization temperature taught by Kool to the method taught by Sampson in view of Nilsen to arrive at the claimed invention with a reasonable expectation for success. While Sampson does not teach specific hybridization temperatures, one

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of ordinary skill in the art would have looked to the prior art for guidance regarding specific and suitable hybridization temperatures. Sampson teaches that circular templates useful in the method comprise rolling circle probes. Kool teaches “the preferred reaction time for rolling circle synthesis is about 1 hour to about 3 days. Preferably, the temperature of the reaction mixture during the rolling circle synthesis is about 20-90 °C” (col. 13, lines 13-22). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the specific hybridization temperature taught by Kool for hybridization and extension of circular templates to the method taught by Sampson in view of Nilsen to arrive at the claimed invention with a reasonable expectation for success.

4. Claim 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN 5, 487,973; January 1996) and Ranki et al. (US Patent 4,563,419; January 1986) as applied to claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 above, and further in view of Wang et al. (US Patent 6,004,775; December 1999). Sampson teaches a method for the amplification of the signal of target sequences using a bidirectional primer and cDNA synthesis (Abstract).

Sampson in view of Nilsen and Ranki teaches all of the limitations of claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 as recited in the rejection above.

With regard to claim 13-15, Nilsen teaches an embodiment of claim 1, wherein the method comprises hybridization buffer (see column 19, lines 14-26), wherein the hybridization buffer comprises 0.25 M NaPO₄, 4.5% SDS, 1 mM EDTA, and 1X SSC (col. 20, lines 60-64, where the hybridization buffer comprises the components of NaPO₄, EDTA and SSC).

However, regarding claim 12, Nilsen does not specifically teach the washing step as comprising specific concentrations of SSC buffers. Regarding claim 14, Nilsen does not specifically teach that the hybridization buffer comprises SDS or additional components. Wang teaches methods of quantitative gene expression analysis using microarrays (Abstract).

With regard to claim 12, Wang teaches an embodiment of claim 11, wherein the washing step further comprises:

a) washing the microarray with 2X SSC buffer containing 0.2% SDS at 55°C for about 10 minutes; b) washing the microarray with 2X SSC buffer at about room temperature for about 10 minutes; and c) washing the microarray with 0.2X SSC buffer at about room temperature for about 10 minutes (col. 10, lines 40-55, where the slides were washed with concentrations of SSC for different incubation times and temperatures).

With regard to claim 13-15, Wang in view of Nilsen teaches an embodiment of claim 1, wherein the method comprises hybridization buffer (col. 10, lines 25-41; col. 6, lines 18-22), wherein the hybridization buffer comprises 4.5% SDS and 1X SSC (col. 10, lines 25-41, where the hybridization buffer comprises 5X SSC and 1% SDS) and further comprises 40% formamide, 4X SSC, and 1% SDS (col. 10, lines 25-41, where the hybridization buffer comprises 5X SSC and 1% SDS; col. 6, lines 18-22).

Furthermore, while Wang, Nilsen and Sampson don't teach the same concentrations of components of the wash buffer or exact hybridization temperatures as claimed, Wang states that the conditions can be varied and an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and buffer component elements and

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concentrations could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific wash buffer was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Sampson and Nilsen, which refer generally to array formats to include the specific washing times and wash buffer compositions of Nilsen in view of Wang to arrive at the claimed invention with a reasonable expectation for success. As taught by Wang, “suitable hybridization conditions are well known to those of skill in the art and reviewed in Maniatis et al, supra, and WO95/21944, where the conditions can be modulated to achieve a desired specificity in hybridization, e.g., highly stringent or moderately stringent conditions” (col. 6, lines 10-22). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Sampson and Nilsen, which refer generally to array formats to include the specific washing times and wash buffer compositions of Nilsen in view of Wang to arrive at the claimed invention with a reasonable expectation for success.

5. Claims 27-28 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sampson et al. (GB 2332516; June 1999 publication) in view of Nilsen et al. (USPN. 5, 487,973; January 1996) and Ranki et al. (US Patent 4,563,419; January 1986) as applied to claims 1-2, 5, 7-11, 13, 35-36, 39 and 41 above, and further in view of Brenner et al. (US Patent 5,846,719; December 1998).

With regard to claims 27-28, 31-32, Brenner teaches a method which comprises dual or multi-channel analysis and wherein the method comprises reverse transcription into cDNA (col. 10, lines 6-9, where the tags incorporated into the signal amplification sequence are fluorescent moieties that may be detected by monitoring the fluorescence emission at defined sets or ranges of wavelengths; see Figure 1, where mRNA is reverse transcribed into cDNA).

With regard to claim 27, 31 and 33, Brenner teaches an embodiment of claim 1-2, 18 and 22, such that said analysis uses two different capture sequences (col. 11, line 61 to col. 12, line 20, where oligonucleotide tags preferably range in length from 18-40 nucleotides and preferably contain at least 100 members, which is more than 2 different capture sequences).

With regard to claim 28 and 32, Brenner teaches an embodiment of claim 1-2, 18 and 22, such that said analysis uses at least three different capture sequences (col. 11, line 61 to col. 12, line 20, where oligonucleotide tags preferably range in length from 18-40 nucleotides and preferably contain at least 100 members, which is more than 3 different capture sequences).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporate the multitude of oligonucleotide tags taught by Brenner into the method of signal amplification taught by Sampson and Nilsen to arrive at the claimed invention with a reasonable expectation for success. Brenner addresses a need in the art by

providing, “an oligonucleotide-based tagging system which provided a large repertoire or tags, but which also minimized the occurrence of false positive and false negative signals without the need to employ special reagents for altering natural base pairing and base stacking free energy differences. Such a tagging system would find applications in many areas, including construction and use of combinatorial chemical libraries, large-scale mapping and sequencing of DNA, genetic identification, medical diagnostics and the like”. Brenner also teaches how this variety of oligonucleotide tags, may be synthesized, including “oligonucleotide tags of the invention are synthesized combinatorially out of subunits between three and six nucleotides in length and selected from the same minimally cross-hybridizing set” (col. 8, lines 50-53). Finally, Brenner notes that “the invention provides a method of labeling and sorting molecules, particularly polynucleotides by the use of oligonucleotide tags” (col. 7, lines 42-44). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to adjust the method taught by Sampson and Nilsen to incorporate the variety of additional oligonucleotide tag sequences taught by Brenner into the primer sequence to arrive at the claimed invention with a reasonable expectation for success.

Response to arguments

Applicant's arguments filed August 13, 2010 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims as lacking written description due to new matter. Applicant argues that “although portions of the disclosure are devoted to teaching prehybridization of the cDNA reagent to the dendrimer... other portions specifically exclude

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mention of prehybridization”. Applicant also argues that “claim 1 itself makes no mention of prehybridization” and points to pages 6 to 7 of the specification as teaching step 2 mixing the cDNA and dendrimer and step 3 recites incubating the mixture with the array and argues that the word prehybridized does not appear in this passage (p. 9 of remarks). Applicant concludes that the specification is consistent with mixing "such that the cDNA reagent is hybridized in a single step to both the microarray and the dendrimer" (p. 9 of remarks) and “thus, one of ordinary skill in the art would have recognized that the invention disclosed recognizes both prehybridization of the cDNA reagent and the dendrimer and simultaneous hybridization of the cDNA reagent to both the microarray and the dendrimer” (p. 10 of remarks).

These arguments have been considered, but are not persuasive. While Applicant’s amendment to remove the phrase “on said microarray” are appreciated, it is noted that the rejection is based on two issues with the claims, the previous phrase and the language of “a single step” of hybridization of all three elements together. While Applicant points to a passage that does not literally use the phrase prehybridization, what is being described in step 2 still describes step of prehybridization of the cDNA and the dendrimer, prior to hybridization to the array. This passage does not support a single step of hybridization, if only because it does not teach a single step that leads to the hybridization of each element as claimed. In the absence of such a teaching, there is not sufficient support for this limitation and the rejection is maintained.

Applicant traverses the rejection of claims 1-17, 27-28, 31-32, 35-36, 39 and 41 as being obvious over Sampson, Nielsen and Ranki. Applicant summarizes the rejection and the basis for establishing a prima facie case of obviousness. Applicant argues “the mixture and microarray

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are mixed at a temperature and for a time sufficient to allow the cDNA to bind to both the microarray and the dendrimer, resulting in the generation of a directly detectable hybridization pattern on the microarray”. Applicant argues “Sampson does not disclose hybridization of cDNA in a single step to both a microarray and to a second component”. Applicant points to Figure 1 and argues that step 1 cDNA is synthesized from mRNA using a bi-directional primer, step 2 the bi-directional primer is used to synthesize signal amplification sequences and in step 3 cDNA is hybridized to an array. Applicant argues “steps 2 and 3 are clearly not done simultaneously” and that it is impossible “to perform steps 2 and 3 together since the conditions for DNA replication are different from those for array hybridization” (p. 12 of remarks). Applicant also argues that the amendment to the claims “specify that dendrimer has at least one first arm comprising a label ‘providing a directly detectable signal’” and argues that the circular template is not labeled and cannot generate a detectable signal and distinguishes over Sampson (p. 12-13 of remarks).

Applicant argues Nilsen and Ranki do not cure the deficiencies of Sampson. Applicant argues “cDNA in Nilsen is not hybridized in a single step to both the microarray and the dendrimer” and “not hybridized at all to an array in Nilsen” and the “sequence to be detected hybridizes between beads A and B – it never hybridizes to the array”. Applicant argues “the nucleic acids to be detected are hybridized to the dendrimers via unique sequences – no common capture sequence is used” (p. 13 of remarks). Finally, regarding Ranki, Applicant summarizes the teaching of Ranki and argues “the problem with the Examiner’s analogy, however, is that the nucleic acids intended to be identified in Ranki, which the Examiner believes corresponds to the cDNA in Sampson (and thus also to the instantly claimed cDNA reagents), do not contain a

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common capture sequence”. Applicant concludes that the fragments bind to different unique sequences and “different labeled fragments must be provided for each assay” and that “the instantly claimed dendrimers, which can bind to any of the cDNAs having the common capture sequence” (p. 14 of remarks).

These arguments have been considered, but are not persuasive. First of all, it is noted that neither Sampson nor Applicant’s method comprise a single step. It is again reiterated that the method of Applicant’s claim 1, for instance, minimally includes a step of pre-hybridizing the cDNA to the dendrimer, followed by a step of hybridization of the cDNA/dendrimer to the microarray, even if the word “prehybridization” is not used, if that is what is occurring it cannot be considered a single step. Next, it is noted that the rejection does not assert that the components hybridize together in a single step in Sampson or that steps 2 and 3 must occur simultaneously. The rejection clearly indicates that Sampson comprises a first component, the cDNA which incorporates the capture sequence, a second component comprising the circular DNA template, that the two are bound together and hybridized and following the binding of the first and second components, the complex is hybridized to the array. The dendrimer element is taught by Nilsen, which can bind to the capture sequence of the 3' end of the cDNA, and considering these elements, the cDNA w/ capture sequence of Sampson, the dendrimer of Nilsen, and the array of Sampson it would have been obvious in view of the suggestion of Ranki to combine the steps of binding the cDNA of Sampson to the dendrimer of Nilsen and the array of Sampson in a single step.

While Applicant’s argument against Sampson as not compatible with the different reaction conditions necessary for steps 2 and 3, it is noted that following step 2, a single cDNA

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product is formed which includes the cDNA and the capture sequence, which mediates binding of the dendrimer of Nilsen, which could all occur in a single step of hybridization. While the rejection teaches that the second component is the circular DNA template (or the signal amplification sequence), this feature is merely a substitute for the dendrimer feature rendered obvious by Nilsen. Next, while Applicant argues that Sampson does not teach a label, this argument is not persuasive because Sampson clearly teaches that label is incorporated into the final product comprising the "second component" signal amplification region and therefore this argument is not persuasive.

Finally, while Applicant argues against Ranki and the logical analogy not being appropriate because Ranki does not teach common capture probes, this argument is not persuasive. While references are considered as a whole, Ranki is not asserted as rendering the capture probes obvious. Instead, Ranki is asserted as rendering obvious the hybridization of multiple components in a single step. The teachings of Ranki would be combined with the common capture probe of Sampson and therefore this line of argument is not persuasive.

Applicant traverses the rejection of claims 3-4, 16-17, 19 and 23-26 as being obvious over Sampson in view of Nilsen, Ranki and Combates. Applicant argues "Examiner has pointed to nothing in Combates that remedies the deficiencies of Sampson, Nilsen and Ranki in this respect" and "cannot render the claimed invention obvious" (p. 15 of remarks).

Applicant traverses the rejection of claim 6 as being obvious over Sampson in view of Nilsen, Ranki and Kool. Applicant argues "Examiner has pointed to nothing in Kool that

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remedies the deficiencies of Sampson, Nilsen and Ranki in this respect” and “cannot render the claimed invention obvious” (p. 15 of remarks).

Applicant traverses the rejection of claims 12-15 as being obvious over Sampson in view of Nilsen, Ranki and Wang. Applicant argues “Examiner has pointed to nothing in Wang that remedies the deficiencies of Sampson, Nilsen and Ranki in this respect” and “cannot render the claimed invention obvious” (p. 16 of remarks).

Applicant traverses the rejection of claims 27-28, 31-32 as being obvious over Sampson in view of Nilsen, Ranki and Brenner. Applicant argues “Examiner has pointed to nothing in Brenner that remedies the deficiencies of Sampson, Nilsen and Ranki in this respect” and “cannot render the claimed invention obvious” (p. 16 of remarks).

Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Wolcott et al. (Clin. Micro. Rev., 1992 5(4):370-386) teaches single step sandwich hybridization (see Figure 2). Wolber et al. (US Patent 6,235,483; May 2001) discloses methods and kits for labeling nucleic acids using tagged oligonucleotides (Abstract).

Conclusion

No claims are allowable. All claims stand rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637